PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference<br>4239-67618-03 | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/US2004/022232 | International filing date *(day/month/year)*<br>09.07.2004 | Priority date *(day/month/year)*<br>09.07.2003 |
| International Patent Classification (IPC) or national classification and IPC<br>A61K33/00, A61P9/08, A61P9/10, A61P9/12 | | |
| Applicant<br>THE GOVERNMENT OF THE UNITED STATES OF AMERICA et | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☒ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 06.05.2005 | 22.07.2005 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office - Gitschiner Str. 103<br>D-10958 Berlin<br>Tel. +49 30 25901 - 0<br>Fax: +49 30 25901 - 840 | Authorized Officer<br>Siatou, E<br>Telephone No. +49 30 25901-327 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/022232



## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

| | |
|---|---|
| **Description, Pages** | |
| 1-60 | as originally filed |
| **Claims, Numbers** | |
| 1-15 | received on 09.05.2005 with letter of 04.05.2005 |
| **Drawings, Sheets** | |
| 1/15-15/15 | as originally filed |

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/022232

## Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

   **see separate sheet**

## Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-15 in respect of Ia

   because:

   ☒ the said international application, or the said claims Nos. 1-15 in respect of IA relate to the following subject matter which does not require an international preliminary examination (specify):

   **see separate sheet**

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

   | | | |
   |---|---|---|
   | the written form | ☐ | has not been furnished |
   | | ☐ | does not comply with the standard |
   | the computer readable form | ☐ | has not been furnished |
   | | ☐ | does not comply with the standard |

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-15 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-15 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | ------ |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)**

International application No.
PCT/US2004/022232



**Re Item I**
Amended claim 1 is allowable.

**Re Item III.**
Claims 1-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V.**
Reference is made to the following documents:
D1 : WO 01/89572 A
D2 : PNAS, vol. 98, no. 22, Oct. 23 2001, pages 12814-12819 (& T. Lauer et al)

The document **D1** is regarded as being the closest prior art to the subject-matter of claim 1, and shows (the references in parentheses applying to this document):
The use of sodium nitrite for topical application (cf. claims 1-35) . Apart from topical treatment, other modes of application (cf. page 12, line 20- page 13, line 11) such as aural, nasal, vaginal, rectal or injectable, depending on the disease to be treated, are also mentioned. Of the diseases to be treated pulmonary hypertension (cf. page 3, lines 5-26) is mentioned.
The subject-matter of claim 1 differs from this known uses in that **non-acidified** sodium nitrite is used.
The subject-matter of claim 1 is therefore new (Article 33(2) PCT).

The problem to be solved by the present invention may be regarded as providing alternative compositions for cardiovascular treatment.

The solution to this problem proposed in claim 1 of the present application, namely the use of non-acidified sodium nitrite, is considered as involving an inventive step (Article 33(3) PCT), for the following reasons.

Unlike **D1**, where the presence of an acid is required in order for the nitric oxide to be released, the present application does not require acidification of the sodium nitrite. In

addition, document **D2**, which was cited by the applicant in the description, states (cf. page 12818, right-hand column, paragraph titled "Nitrite as delivery source of Intravascular NO") that intraarterial infusion of nitrite showed a complete lack of vasodilator action.

Claims 2-15 are dependent on claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

For the assessment of the present claims 1-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLAIMS

1. A method for treating or ameliorating a condition selected from:

(a) hepatic or cardiac or brain ischemia-reperfusion injury;

(b) pulmonary hypertension; or

(c) cerebral artery vasospasm,

in a subject by decreasing blood pressure and/or increasing vasodilation in the subject, the method comprising administering non-acidified sodium nitrite to the subject to decrease the blood pressure and/or increase vasodilation in the subject, thereby treating or ameliorating the condition.

2. The method of claim 1, which is a method for treating or ameliorating hepatic or cardiac or brain ischemia-reperfusion injury.

3. The method of claim 2, wherein administering sodium nitrite to the subject is intravenous.

4. The method of claim 2 or 3, wherein the sodium nitrite is administered to a circulating concentration of about 0.6 to 240 μM.

5. The method of claim 1, which is a method for treating or ameliorating pulmonary hypertension.

6. The method of claim 5, wherein the pulmonary hypertension is neonatal pulmonary hypertension.

7. The method of claim 5 or 6, wherein administering sodium nitrite to the subject is by inhalation.

8. The method of claim 7, wherein the sodium nitrite is nebulized.

9. The method of any one of claims 5 through 8, wherein the sodium nitrite is administered at a rate of 270 μmol/minute.

10. The method of claim 1, which is a method for treating or ameliorating cerebral artery vasospasm.

11. The method of claim 10, wherein administering sodium nitrite to the subject is intravenous.

12. The method of claim 10 or 11, wherein the sodium nitrite is administered at a rate of about 45 to 60 mg/kg.

13. The method of any one of claims 1-12, wherein the sodium nitrite is administered in combination with at least one additional agent.

14. The method of any one of claims 1-13, wherein the subject is a mammal.

15. The method of any one of claims 14, wherein the subject is a human.

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